#14 m.m. 6/12/03

Docket No. JANS-0008
~~JAB1461~~

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	McGee, et. al.	
Serial No.	:	09/868,991	Art Unit: 1615
Filed	:	July 26, 2001	Examiner: Pulliam, A. E.
For	:	Controlled-Release Galantamine Composition	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on

March 6, 2003
(Date)

Matthew B. Zisk (Reg. No. 45,257)
Name of applicant, assignee, or Registered Representative

(Signature)

March 6, 2003
(Date of Signature)

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF LUC TRUYEN, M.D. Ph.D. UNDER 37 C.F.R § 1.132

I, Luc Truyen, declare as follows:

1) I am a citizen of Belgium and hold the position of Senior Director Clinical R&D at Johnson & Johnson Pharmaceutical Development L.L.C ("J&JPRD")

2) I did my undergraduate studies in Medicine at the University of Antwerp, Belgium where I received a Bachelor's degree in 1985. I did my medical studies at the University of Antwerp where I received a M.D. degree in 1989. I did my

graduate studies in medical sciences at the University of Antwerp where I received a Ph.D. degree in 1996.

3) Since completing my studies, I have held the following positions:

1994-1996: Research fellow at the Dutch Magnetic Resonance Imaging in Multiple Sclerosis research unit , 'Vrije Universiteit', Amsterdam, The Netherlands from October 1994 to September 1996;

1994-1998: Supervisor and coordinator MS-Rehabilitation unit, Clinic "De Mick", Brasschaat: from October 1994 to April 1998: a 40-bed rehab unit for multiple sclerosis and neurodegenerative diseases;

1996-1998: Attending neurologist, Neurology dept., University Hospital Antwerp from September 1996 to April 1998, responsible for the MS outpatient clinic and supporting the Neurophysiology clinic and the residents training programme;

~~1998-present: Joined Janssen Research Foundation (now J&JPRD) in 1998 as~~ Associate Director, CNS R&D. Promoted to Director, CNS R&D in August 2000. Promoted to Senior Director July 2001.

4) I am a member of the the Born-Bunge Foundation, rang A, an Associated member of the Belgian Neurological Society, Vice-chairman of the MS research council of Belgium (WOMS), a Founding member of the American Society for Experimental Neurotherapeutics (ASENT), and an Editorial Board member of 'NeuroRX', a new journal founded by ASENT. I have published or delivered over 75 papers in peer-reviewed journals and at scientific symposia and conferences.

5) I am fluent in the English language. I have read and understood the specification and claims of United States Patent Application Number 09/868,991 and the Office Action pertaining to it mailed September 27, 2002.

6) As part of my duties at J&JPRD, I help to design, coordinate and analyze the results of clinical studies on galantamine hydrobromide (Reminyl®). Between February 2001 and October 2001, I oversaw the conduct, analyis and reporting of the GAL-NED-8 clinical trials. Between February 2001 and January 2003, I oversaw the conduct, analysis and reporting of the GAL-INT-10 clinical trials. As discussed in detail below, data from these clinical trials show that, surprisingly and unexpectedly, the incidences of nausea and vomiting in subjects taking a galantamine controlled-release ("CR") composition falling under the claims of the current application are greatly reduced over the incidences of these adverse events in subjects taking a galantamine immediate-release ("IR") formulation, and also that this reduction is tied to the rate of rise in blood plasma concentration rather than to the maximum blood plasma concentration of galantamine.

GAL-NED-8

7) In randomized, double-blind, placebo-controlled Phase 3 studies conducted in the clinical program for galantamine IR, a dose of 16 or 24 mg/day was shown to be safe and effective in treating patients with mild to moderate Alzheimer's Disease ("AD"), and, relative to placebo, produced significant cognitive improvement as early as 3 weeks.

8) In this program, galantamine-treated subjects in 5 placebo-controlled studies of 3 or 6 months' duration showed an improvement in cognitive and global performance relative to placebo. Continued effectiveness of galantamine IR was demonstrated in subjects receiving up to 4 years of treatment in open-label extension studies when compared with the rate of decline predicted from historical data in untreated patients with mild to moderate AD.

9) With the commercial galantamine IR used in the study, >80% of active drug is released from the tablet within 20 to 40 minutes of oral administration. The most common adverse events (in more than 5 % of subjects receiving galantamine IR 12 mg twice daily, b.i.d.) in large-scale, placebo-controlled studies of 6 months' duration were nausea, vomiting, dizziness, anorexia, headache, diarrhea, and

weight decrease. The frequency of each of these adverse events was greater in galantamine- than in placebo-treated subjects. Moreover, dose-related increases were reported in the frequency of nausea, vomiting, diarrhea, abdominal pain, dizziness, anorexia, and headache.

10) During the development of galantamine IR during the period of 1995-1999, a weekly dose escalation scheme resulted in significant gastrointestinal adverse events. The later introduction in 2000 of a 4-week dose escalation scheme with galantamine IR resulted in increased tolerability of that formulation.

11) In 1998, a program to develop a once-daily (q.d.) controlled-release galantamine formulation was initiated. The galantamine-CR capsule formulation that came out of this program delivers 25% of the total galantamine dose as an IR dose, and the remaining 75% of the total dose as a controlled-release dose. This formulation was shown to be bioequivalent to the currently approved IR formulation in terms of area under the plasma concentration-time curve (AUC) and minimum plasma concentration (C_{min}) but not the maximum plasma concentration (C_{max}).

12) As part of the galantamine CR program, a Phase 3 study with the CR formulation employed a 4-week dose escalation scheme and a once-daily dosing regimen of galantamine CR. In one of the standard pharmacokinetic ("PK") trials of GAL-NED-8 run in 24 healthy volunteers the following observations were made: **Figure 1** shows the plasma concentration profile of the IR formulation (open circles) compared to an equal daily dose of the CR formulation (closed circles); the most frequent adverse events are also tabulated in this figure from which it is clear that there is a significant reduction of the occurrence of these adverse events when using the CR formulation.

13) What is particularly surprising and unexpected about this reduction in adverse events is that the differences between CR and IR in aggregate are not tied to the C_{max}. As **Figures 2a** and **2b** show, the highest incidence of adverse events is reported at the 30 minute time point for the IR (which has T_{max} at 1-1½ hr) whereas the CR shows no significant peak in adverse events with time (C_{max} is

between 3-4hrs). These results indicate that the differences in adverse events rates are tied to differences in rate of rise in plasma level between the two formulations rather than simple differences in C_{max}.

GAL-INT-10

14) A single, pivotal efficacy and safety study was conducted in the clinical program for galantamine CR. This was Study GAL-INT-10, presented as an adequate and well-controlled study to support the claimed use of galantamine CR in treating mild-to-moderate AD. The primary objective of the GAL-INT-10 study was to evaluate the efficacy and safety of flexible once-daily doses of galantamine CR 16 or 24 mg/day compared with placebo. There were 3 treatment arms: galantamine CR, galantamine IR (active comparator), and placebo. In total 965 patients were available for a safety analysis. From an analysis of the safety data as depicted in **Figure 3**, consistent with the results of the GAL-NED-8 study discussed above, the actual number of episodes of nausea and vomiting were lower during dose escalation for the controlled release formulation compared to the immediate release formulation.

15) In this study, study physicians were permitted to decide whether any given patient should increase the study medication at week 8 from 16 mg/day to 24 mg/day. Fewer patients in the IR arm escalated to 24 mg/day than in the CR arm.

16) In the upper panel of Figure 3 at week 8 there is a sudden increase in nausea for the CR form. This increase is caused by the fact that more patients were able to go up to the highest dose of 24 mg/d with the CR formulation compared to the IR formulation.

17) Results from this study relating to the decrease in adverse events are difficult to distinguish because no PK samples were taken. Furthermore, this trial, as with phase III trials in general, does not have a high degree of time resolution. Finally, the adverse event benefit for the controlled release formulation in this trial is hidden in standard adverse event reporting tables which only reflect the numbers

of patients by treatment who have at least once reported an adverse event rather than quantifying how many events have occurred per patient.(see **Table 7** from the regulatory submission appended to this declaration).

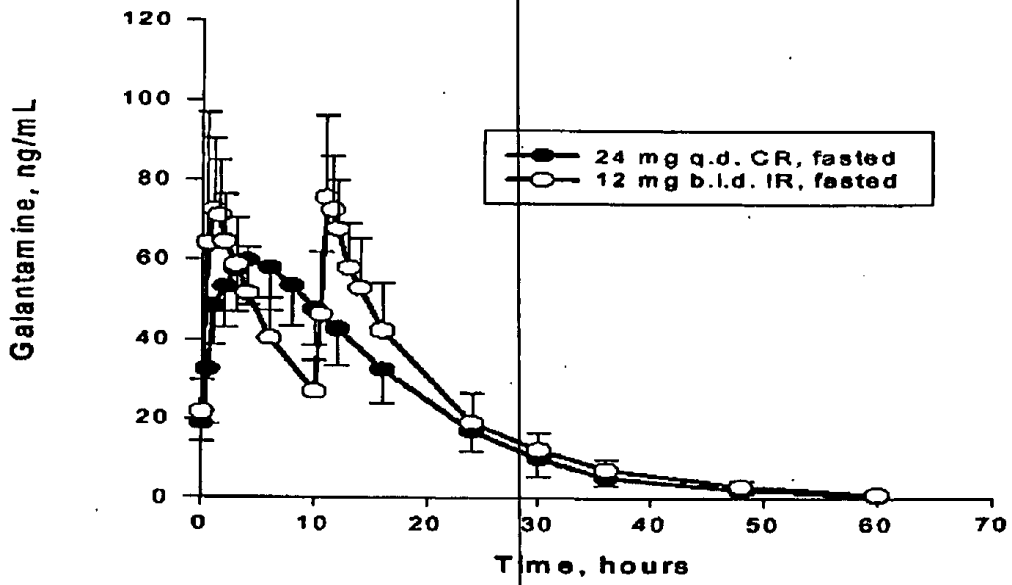
18) All statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true. All statements in this declaration are made with the knowledge that willful false statements and the like if made in this declaration are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity or enforceability of any patent that may issue on the application for which this declaration is made.

Dated this 4th day of March, 2003

Luc Truyen, M.D. Ph.D.

Figure 1: Plasma levels and Adverse Events IR vs. CR

Reminyl CR Phase I PK Trial GAL-NED-8
Once Weekly Dose Escalation up to 24 mg/d



	CR 24mg QD/F	IR 12mg BID/F
Nausea	27.3%	45.5%
Somnolence	0.0%	9.1%
Dizziness	13.6%	63.6%

Figure 2a: Time course after intake of adverse event reporting part 1-nausea & vomiting

Reminyl CR Phase I PK Trial GAL-NED-8
Once weekly dose escalation up to 24 mg/d
nausea & vomiting

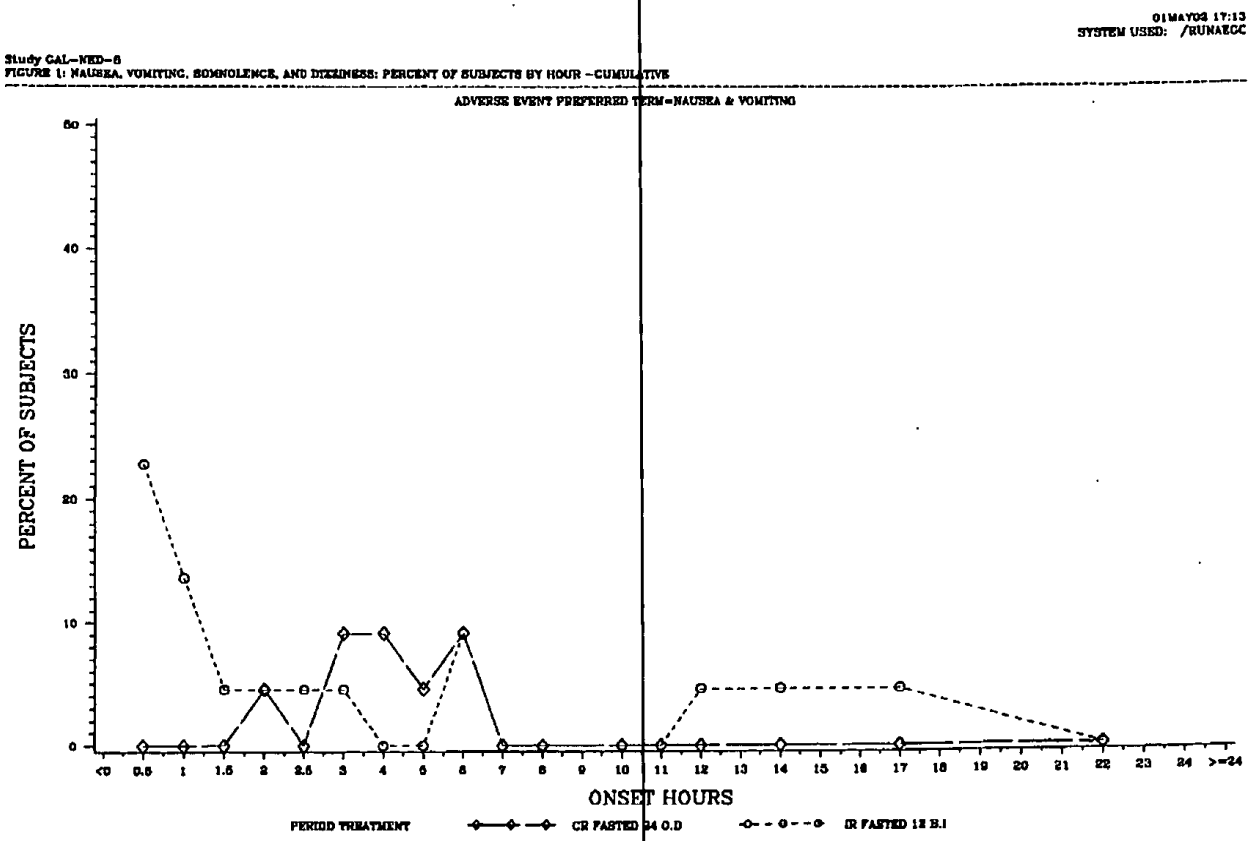


Figure 2b: Time course after intake of adverse event reporting part 2-Dizziness

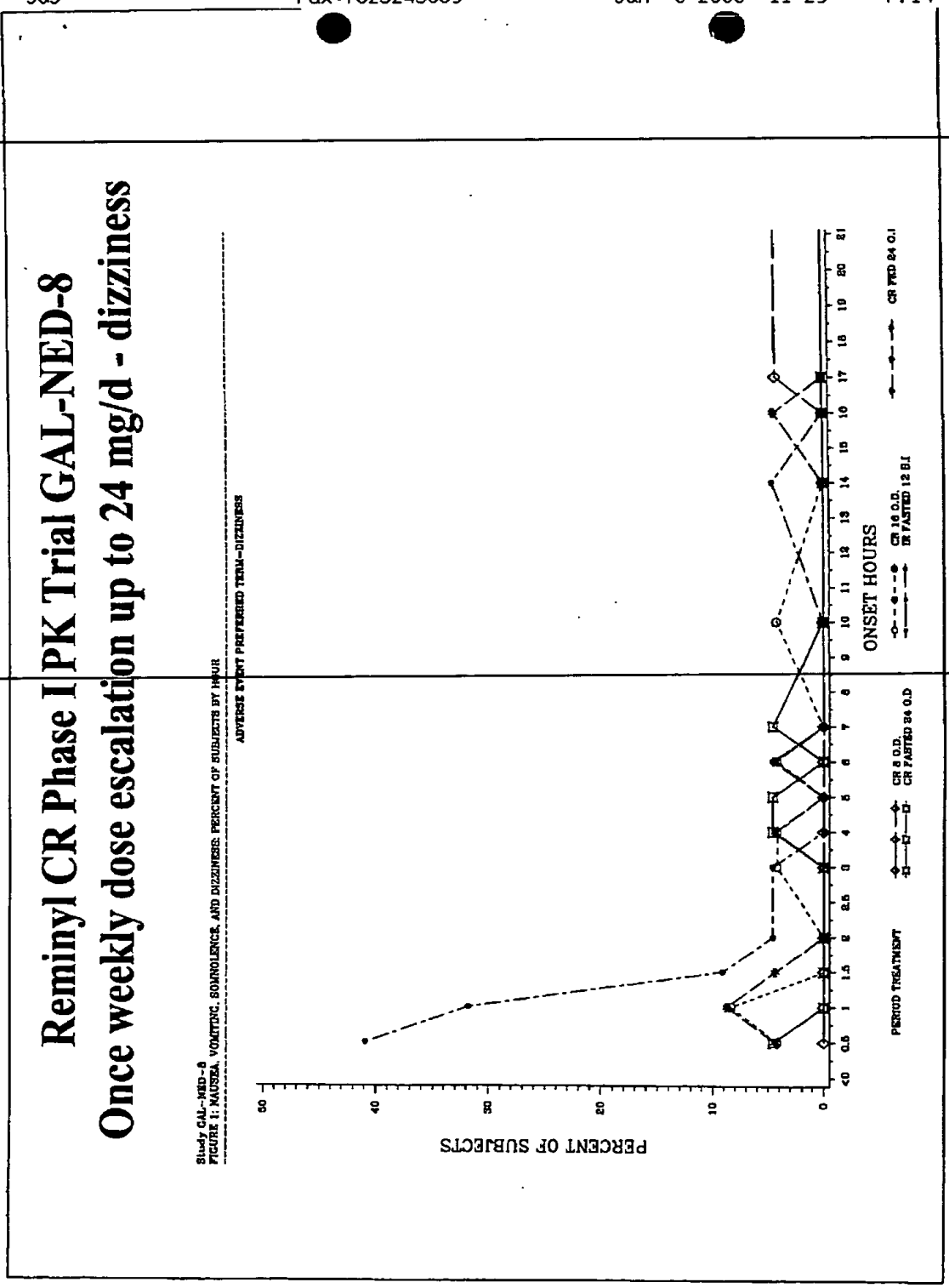
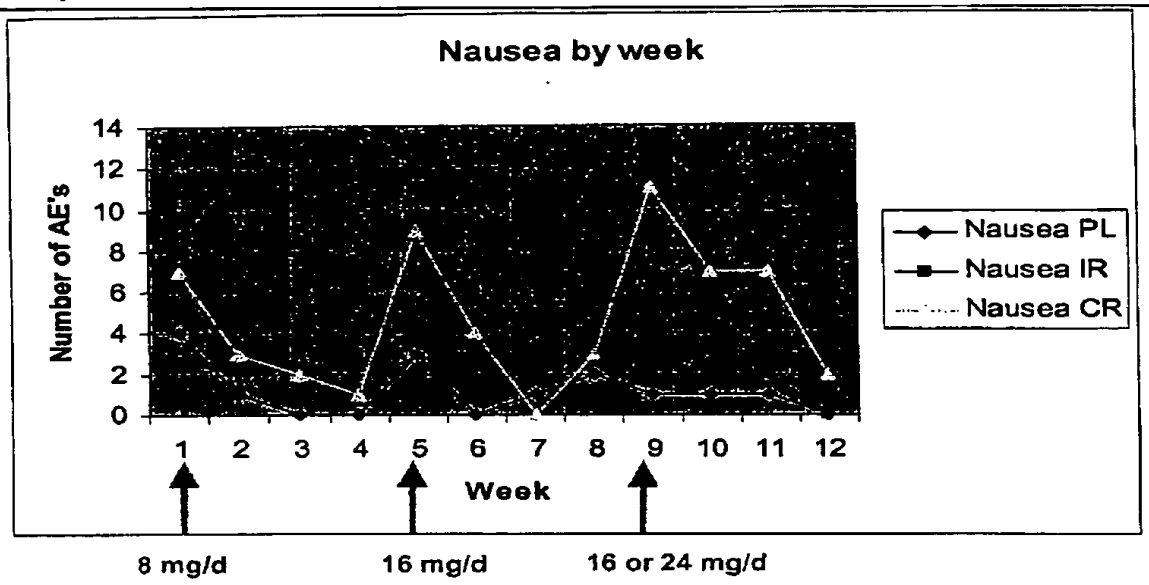


Figure 3: Reminyl CR Phase III Trial GAL-INT-10 :Nausea and Vomiting during Dose Escalation



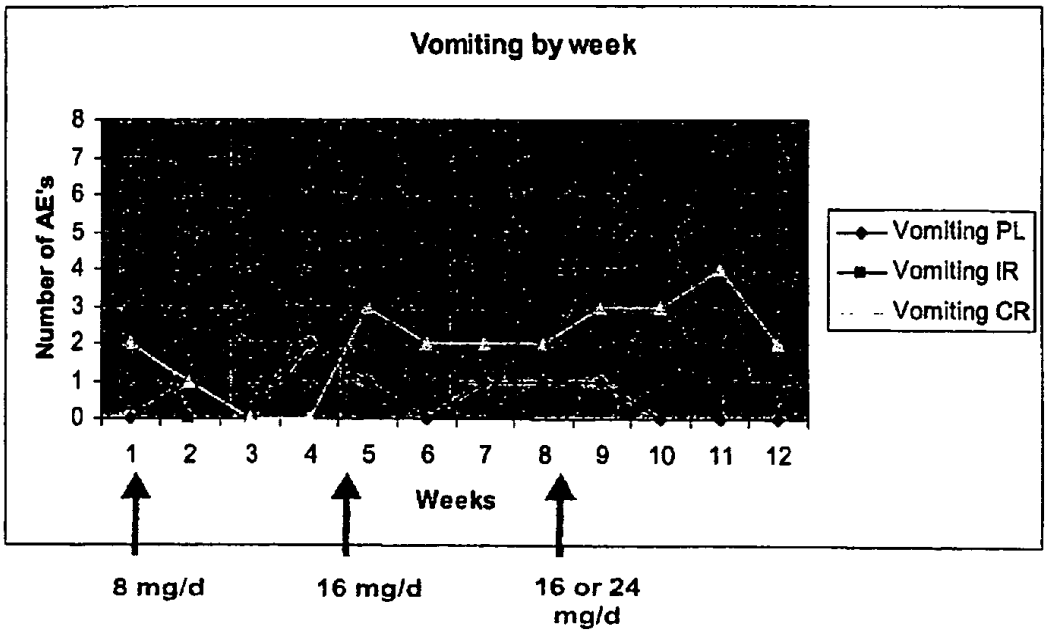


Table 7: Incidence ≥5% of Adverse Events in any Treatment Group by World Health Organization System Organ Class and Preferred Term—Treatment-Emergent Analysis
(GAL-INT-10: All Randomized and Treated Subjects Analysis Set)

System Organ Class Preferred Term	Placebo (N=320) n (%)	GAL-IR (N=326) n (%)	GAL-CR (N=319) n (%)	Total (N=965) n (%)
Total no. subjects with adverse events	224 (70)	235 (72)	253 (79)	712 (74)
Gastrointestinal system disorders	72 (23)	92 (28)	92 (29)	256 (27)
Nausea	16 (5)	45 (14)	54 (17)	115 (12)
Diarrhea	22 (7)	22 (7)	15 (5)	59 (6)
Vomiting	7 (2)	28 (9)	21 (7)	56 (6)
Psychiatric disorders	74 (23)	80 (25)	92 (29)	246 (25)
Agitation	21 (7)	20 (6)	22 (7)	63 (7)
Anorexia	8 (3)	22 (7)	19 (6)	49 (5)
Depression	8 (3)	16 (5)	18 (6)	42 (4)
Body as a whole - general disorders	60 (19)	62 (19)	76 (24)	198 (21)
Injury	18 (6)	12 (4)	24 (8)	54 (6)
Centr & periph nervous system disorders	52 (16)	69 (21)	77 (24)	198 (21)
Dizziness	14 (4)	24 (7)	33 (10)	71 (7)
Headache	18 (6)	18 (6)	27 (8)	63 (7)
Respiratory system disorders	43 (13)	41 (13)	45 (14)	129 (13)
Upper respiratory tract infection	16 (5)	12 (4)	15 (5)	43 (4)
Metabolic and nutritional disorders	36 (11)	43 (13)	42 (13)	121 (13)
Weight decrease	4 (1)	17 (5)	14 (4)	35 (4)
Urinary system disorders	38 (12)	39 (12)	40 (13)	117 (12)
Urinary tract infection	26 (8)	22 (7)	22 (7)	70 (7)
Secondary terms	39 (12)	30 (9)	28 (9)	97 (10)
Fall	19 (6)	20 (6)	20 (6)	59 (6)